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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/562,762	12/27/2005	Massimo Ferrari	207,385	8763

7590 10/06/2008

Jay S Cinamon
Abelman Frayne & Schwab
10th Floor
666 Third Avenue
New York, NY 10017

EXAMINER	
MABRY, JOHN	

ART UNIT	PAPER NUMBER
1625	

MAIL DATE	DELIVERY MODE
10/06/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/562,762	FERRARI ET AL.	
	Examiner	Art Unit	
	John Mabry, PhD	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 September 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *26-46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *26-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Request for Continued Examination

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on September 17, 2008 has been entered.

Applicant's response on September 17, 2008 filed in response to the Non-Final Office Action dated March 17, 2008 has been received and duly noted. Applicants arguments are not persuasive. Examiner is maintaining the obviousness rejection of claims 26-45 as being unpatentable over Jones et al (US 4,358,593) in view of Jones et al (EP62503) and in further view of Alt (US 5,523,416). It would be obvious to one of ordinary skill in the art to deprotect acetoxy compounds of formula VI and make the HCl salt form of final product I, especially in view of the prior art teachings disclosed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 26-46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jones et al (US 4,358,593) in view of Jones et al (EP62503) and in further view of Alt (US 5,523,416).

The instant application claims a process for the preparation of raloxinfene hydrochloride by reaction of 6-methoxy-2-(4-methoxyphenyl)benzo[b]thiophene to make 6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thiophene then protecting with an acetylating agent, particularly acetic anhydride in presence of triethyl amine, to produce the corresponding 6-acetoxy-2-(4-acetoxyphenyl)benzo[b]thiophene. The 6-acetoxy-2-(4-acetoxyphenyl)benzo[b]thiophene is acylated with 4-(2-piperidinoethoxy)benzoylchloride hydrochloride with aluminum chloride in halogenated solvent, in particularly methylene chloride, to obtain 6-acetoxy-2-(4-acetoxyphenyl)-3-[4-(2-piperdinoethoxy)benzoyl]-benzo[b]thiophene without isolating the product. The 6-acetoxy-2-(4-acetoxyphenyl)-3-[4-(2-piperdinoethoxy)benzoyl]-benzo[b]thiophene is deprotected by hydrolysis with treatment of alkaline hydroxide in alcohol solvent, in particular sodium hydroxide followed by treatment of strong acid, particularly hydrochloric acid to obtain the corresponding 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzo[b]thiophene hydrochloride (raloxifene hydrochloride).

Scope & Content of Prior Art MPEP 2141.01

Jones et al (US 4,358,593 – see entire disclosure) discloses a process for the preparation of raloxinfene hydrochloride by reaction of 6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thiophene with acetylating agent, particularly acetic anhydride in the presence of 4-dimethylaminopyridine (but also teaches the use of triethyl amine, see

column 3, lines 34-43), to produce the corresponding 6-acetoxy-2-(4-acetoxyphenyl)benzo[b]thiophene (see column 9, Preparation 2). The 6-acetoxy-2-(4-acetoxyphenyl)benzo[b]thiophene is acylated with 4-(2-piperidinoethoxy)benzoylchloride hydrochloride with aluminum chloride in halogenated solvent, in particularly methylene chloride, to obtain 6-acetoxy-2-(4-acetoxyphenyl)-3-[4-(2-piperdinoethoxy)benzoyl]-benzo[b]thiophene hydrochloride in which a small portion was recrystallized to from ethanol to provide an analytical sample. The 6-acetoxy-2-(4-acetoxyphenyl)-3-[4-(2-piperdinoethoxy)benzoyl]-benzo[b]thiophene was then deprotected by treatment of sodium hydroxide in methanol, followed by acidification to pH 2-3 then readjusted to basic pH 8 which resulted in 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzo[b]thiophene (raloxifene) (see column 12, lines 36-65, Example 9).

Differences between Prior Art & the Claims MPEP 2141.02

Jones et al (US 4,358,593) differs from the instant invention in that Jones does not disclose the direct synthesis of 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzo[b]thiophene hydrochloride (raloxifene hydrochloride). However, Jones et al suggests that during the deprotection of 6-acetoxy-2-(4-acetoxyphenyl)-3-[4-(2-piperdinoethoxy)benzoyl]-benzo[b]thiophene to 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzo[b]thiophene (raloxifene), it is convenient to form the salts by reacting the 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzo[b]thiophene (raloxifene) with a suitable acid wash in the final step of the synthesis to achieve high

yields of corresponding salt. The suitable acid is preferably hydrochloric acid (see column 8, lines 8-30).

Jones et al differs also from the instant invention in that Jones does not disclose the synthesis of 6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thiophene by demethylation of the starting material 6-methoxy-2-(4-methoxyphenyl)benzo[b]thiophene.

However, Jones et al (EP62503) teaches that 6-methoxy-2-(4-methoxyphenyl)benzo[b]thiophene can undergo acylation with 4-(2-piperidinoethoxy)benzoylchloride hydrochloride to form the protected intermediate which can eventually be synthesized to the desired product (see page 2, line 25 – page 4, line 6).

Additionally, Alt (US 5,523,416) has also shown that 6-methoxy-2-(4-methoxyphenyl)benzo[b]thiophene can be deprotected with pyridine hydrochloric acid to make the 6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thiophene (see column 14, lines 61-67 through column 15, lines 1-9, Example 2).

Prima Facie Obviousness, Rational & Motivation MPEP 2142-2413

It would be obvious to one of ordinary skill in the art at the time when the invention was made to initiate the synthesis of the desired final product, 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzo[b]thiophene hydrochloride (raloxifene hydrochloride) by Jones' (US 4,358,593) procedure by changing the starting material, 6-methoxy-2-(4-methoxyphenyl)benzo[b]thiophene, which is taught in the EP62503 reference in the process of making the same compound.

The adjustment of particular conventional working conditions (e.g. determining result effective amounts of the ingredients beneficially taught by the cited references), as well as adjustment of reaction temperature, reaction time and use of solvents, interchanging a particular acid and/or base, not isolating intermediates, is deemed merely a matter of judicious selection and routine optimization which is well within the purview of the skilled artisan (*In re* Mostovych, Weber, Mitchell and Aulbach, 144 USPQ 38). Accordingly, these types of modifications would have been well within the purview of the skilled artisan and no more than an effort to optimize results.

New Rejection

Claims 26-46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Alt (US 5,512,684).

The instant application claims a process for the preparation of raloxinfene hydrochloride (I) by reaction of 6-methoxy-2-(4-methoxyphenyl)benzo[b]thiophene (II) to make 6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thiophene (III) then protecting with an acetylating agent, particularly acetic anhydride in presence of triethyl amine, to produce the corresponding 6-acetoxy-2-(4-acetoxyphenyl)benzo[b]thiophene (IV). The 6-acetoxy-2-(4-acetoxyphenyl)benzo[b]thiophene (IV) is acylated with 4-(2-piperidinoethoxy)benzoylchloride hydrochloride with aluminum chloride in halogenated solvent, in particularly methylene chloride, to obtain 6-acetoxy-2-(4-acetoxyphenyl)-3-[4-(2-piperdinoethoxy)benzoyl]-benzo[b]thiophene (VI) without isolating the product. The 6-acetoxy-2-(4-acetoxyphenyl)-3-[4-(2-piperdinoethoxy)benzoyl]-benzo[b]thiophene is

deprotected by hydrolysis with treatment of alkaline hydroxide in alcohol solvent, in particular sodium hydroxide followed by treatment of strong acid, particularly hydrochloric acid to obtain the corresponding 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzo[b]thiophene hydrochloride (raloxifene hydrochloride, I).

Scope & Content of Prior Art MPEP 2141.01

Alt describes a process as illustrated in Scheme III (columns 5/6) for the preparation of raloxinfene hydrochloride (I) by reaction of 6-methoxy-2-(4-methoxyphenyl)benzo[b]thiophene (II) (R=C1-C6 alkyl, column 2, lines 8-9 and see "Dealkylation" in column 7) to make 6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thiophene (III) then protecting with an acetylating agent, particularly acetic anhydride in presence of triethyl amine, to produce the corresponding 6-acetoxy-2-(4-acetoxyphenyl)benzo[b]thiophene (IV) (see "Reprotection" in bottom of column 7 column 8, lines 1-5). The 6-acetoxy-2-(4-acetoxyphenyl)benzo[b]thiophene (IV) is acylated with 4-(2-piperidinoethoxy)benzoylchloride hydrochloride with aluminum chloride in halogenated solvent, in particularly methylene chloride, to obtain 6-acetoxy-2-(4-acetoxyphenyl)-3-[4-(2-piperdinoethoxy)benzoyl]-benzo[b]thiophene (VI) then isolating the crude product (see "Acylation" in column 9, lines 22-23, lines 37-41). The 6-acetoxy-2-(4-acetoxyphenyl)-3-[4-(2-piperdinoethoxy)benzoyl]-benzo[b]thiophene (VI) is deprotected by hydrolysis with treatment of alkaline hydroxide in alcohol solvent, in particular sodium hydroxide followed by treatment of strong acid, particularly hydrochloric acid to obtain the corresponding 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzo[b]thiophene hydrochloride (raloxifene hydrochloride, I) (see

"Deprotection of Reprotected Dihydroxythiophenes" in bottom of column 10 - column 11, lines 1-5 and lines 28-39).

Differences between Prior Art & the Claims MPEP 2141.02

Alt differs from the instant application in the following ways. Alt isolates the crude product, 6-acetoxy-2-(4-acetoxyphenyl)-3-[4-(2-piperdinoethoxy)benzoyl]-benzo[b]thiophene (VI) prior to converting to desired product (I) versus Applicant's did not isolate 6-acetoxy-2-(4-acetoxyphenyl)-3-[4-(2-piperdinoethoxy)benzoyl]-benzo[b]thiophene (VI).

Additionally, the instant application describes the purity (and impurities) of products in claimed process.

Prima Facie Obviousness, Rational & Motivation MPEP 2142-2413

It would be obvious to one of ordinary skill in the art at the time when the invention was made to initiate the synthesis of the desired final product, 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzo[b]thiophene hydrochloride (raloxifene hydrochloride) by Alt. The procedure, steps of synthesis and reactions conditions are all described that would motivate one of ordinary skill in the art to make minor and obvious experimental adjustment in order to achieve high yields and high purity of desire product, (I).

The adjustment of particular conventional working conditions (e.g. determining result effective amounts of the ingredients beneficially taught by the cited references), as well as adjustment of reaction temperature, reaction time and use of solvents,

interchanging a particular acid and/or base, not isolating intermediates, is deemed merely a matter of judicious selection and routine optimization which is well within the purview of the skilled artisan (*In re* Mostovych, Weber, Mitchell and Aulbach, 144 USPQ 38). Accordingly, these types of modifications would have been well within the purview of the skilled artisan and no more than an effort to optimize results.

The key to supporting any rejection under 35 U.S.C. 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious. The Supreme Court in KSR noted that the analysis supporting a rejection under 35 U.S.C. 103 should be made explicit. The Court quoting In re Kahn, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006), stated that "[R]ejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.'" KSR, 550 U.S. at___, 82 USPQ2d at 1396. Exemplary rationales that may support a conclusion of obviousness include:

(A) Combining prior art elements according to known methods to yield predictable results;

(B) Simple substitution of one known element for another to obtain predictable results;

(C) Use of known technique to improve similar devices (methods, or products) in the same way;

(D) Applying a known technique to a known device (method, or product) ready for improvement to yield predictable results;

(E) "Obvious to try" – choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success;

(F) Known work in one field of endeavor may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations are predictable to one of ordinary skill in the art;

(G) Some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention. See MPEP § 2143 for a discussion of the rationales listed above along with examples illustrating how the cited rationales may be used to support a finding of obviousness. See also MPEP § 2144- §2144.09 for additional guidance regarding support for obviousness determinations.

The aforementioned reasons above describe rationales that support a conclusion of obviousness based upon the KSR International Co. *v.* Teleflex Inc. decision. Letters (A) - (E) rationale is supported above.

Status of the Claims

Claims 26-46 stand rejected.

Claim 46 is new.

Conclusion

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to John Mabry, PhD whose telephone number is (571) 270-1967. The examiner can normally be reached on M-F from 9am to 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's primary examiner can be reached at (571) 272-0684, first, or the Examiner's supervisor, Janet Andres, PhD, can be reached at (571) 272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

/John Mabry/
Examiner
Art Unit 1625

/Rita J. Desai/
Primary Examiner, Art Unit 1625